CLAIMS

- 1. A pharmaceutical composition for therapeutic or prophylactic administration to a subject having an infective disease or at risk for contracting an infective disease, the composition comprising an aqueous carrier having in solution therein (a) a benzoquinolizine-2-carboxylic acid antimicrobial drug or salt, polymorphic form, enantiomeric form, other isomeric or racemic form thereof in a therapeutically or prophylactically effective drug concentration that is above the practical limit of solubility of the drug in a substantially isotonic aqueous solution at a physiologically compatible pH, and (b) a pharmaceutically acceptable solubilising agent selected from a basic aminoacid, a cyclodextrin, a cyclodextrin polymer or derivative theref or a mixture thereof in a concentration sufficient to maintain the drug in solution at drug concentration that is above the practical limit of solubility of the drug in a substantially isotonic aqueous solution at a physiologically compatible pH.
- 2. The composition of claim 1, that is suitable for parenteral administration.
- 3. The composition of claim 1, that is suitable for intravenous injection or infusion.
- 4. The composition of claim 1, wherein the concentration of a drug is about 1 mg/ml to about 100 mg/ml.
- 5. The composition of claim 1, wherein the concentration of a drug is about 4 mg/ml to about 12 mg/ml.
- 6. The composition of claim 1, wherein the concentration of a drug is about 5 mg/ml to about 9 mg/ml.
- 7. The composition of claim 1, wherein the benzoquinolizine-2-carboxylic acid antimicrobial drug is selected from a compound of the formula:

$$R_{8}$$
 R_{5}
 R_{10}
 R_{10}

wherein:

 R_5 is C_{1-6} alkyl, as a mixture of enantiomers or in a stereochemical orientation;

 R_8 is 4-hydroxypiperidinyl optionally further substituted with one or more C_{1-6} alkyl, hydroxypiperidinyl optionally further mono/poly substituted with C_{1-6} alkyl;

R₁₀ is selected from H, C₁₋₅ alkyl, amino, alkylamino or acylamino group; or an optical isomer, diastereomer or enantiomer thereof, or a polymorph, pseudopolymorph or a prodrug thereof or pharmaceutically acceptable salt or hydrate thereof or a mixture thereof.

8. The composition of claim 7 wherein in the formula (I), R_5 is CH_3 , in S-orientation. R_8 is

$$R_2$$
 R_1
 N

wherein:

R is hydrogen, C_1 - C_6 alkyl, glycosyl, aralkyl, C_1 - C_6 alkanoyl, or aminoalkanoyl or R is $C_6H_{11}O_6$, PO_3H_2 or SO_3H thus giving respectively the gluconic acid, phosphoric acid and sulfonic acid ester derivatives of the compounds;

 R_1 and R_2 are the same or different and are selected from H, C_{14} alkyl, aralkyl, aminoalkyl, trifluoroalkyl or halogen;

 R_4 is H, C_{1-4} alkyl, CF_3 , phenyl, or F; R_4 is present at one or more of the positions of 2-, 4-, 5-, or 6- of the piperidine ring; and

R₁₀ is selected from H, C₁₋₅ alkyl, amino, alkylamino or acylamino groups.

9. The composition of claim 7, wherein the benzoquinolizine-2-carboxylic acid antimicrobial drug is selected from the group consisting of:

RS-(±)-9-fluoro-6,7-dihydro-8-(4-hydroxypiperidin-1-yl)-5-methyl-1-oxo-1H,5H-benzo [i,j]quinolizine-2-carboxylic acid;

R(+)-9-fluoro-6,7-dihydro-8-(4-hydroxypiperidin-1-yl)-5-methyl-1-oxo-1H,5H-benzo [i,j]quinolizine-2-carboxylic acid;

S-(-)-9-fluoro-6,7-dihydro-8-(4-hydroxypiperidin-1-yl)-5-methyl-1-oxo-1H,5H-benzo [i,j]quinolizine-2-carboxylic acid;

RS-(±)-9-fluoro-6,7-dihydro-8-(4-hydroxypiperidin-1-yl)-5-methyl-1-oxo-1H,5H-benzo [i,j]quinolizine-2-carboxylic acid arginine salt and solvatomorphic or polymorphic forms thereof;

R(+)-9-fluoro-6,7-dihydro-8-(4-hydroxypiperidin-1-yl)-5-methyl-1-oxo-1H,5H-benzo [i,j]quinolizine-2-carboxylic acid arginine salt and solvatomorphic or polymorphic forms thereof;

S-(-)-9-fluoro-6,7-dihydro-8-(4-hydroxypiperidin-1-yl)-5-methyl-1-oxo-1H,5H-benzo [i,j]quinolizine-2-carboxylic acid arginine salt and solvatomorphic or polymorphic forms thereof;

RS-(±)-9-fluoro-6,7-dihydro-8-(4-hydroxypiperidin-1-yl)-5-methyl-1-oxo-1H,5H-benzo [i,j]quinolizine-2-carboxylic acid 0.2 hydrate;

R(+)-9-fluoro-6,7-dihydro-8-(4-hydroxypiperidin-1-yl)-5-methyl-1-oxo-1H,5H-benzo [i,j]quinolizine-2-carboxylic acid 0.2 hydrate;

S-(-)-9-fluoro-6,7-dihydro-8-(4-hydroxypiperidin-1-yl)-5-methyl-1-oxo-1H,5H-benzo [i,j]quinolizine-2-carboxylic acid 0.2 hydrate;

S-(-)-9-fluoro-6,7-dihydro-8-{trans-4-(RS)-hydroxy-3-(RS)-

methylpiperidin-1-yl}-5-methyl-1-oxo-1H,5H-benzo[i,j]quinolizine-2-carboxylic acid;

S-(-)-9-fluoro-6,7-dihydro-8-{cis-4-(RS)-hydroxy-3-(RS)-methylpiperidin-1-yl-5-methyl-oxo-1H,5H-benzo[i, j]quinolizine-2-carboxylic acid;

S-(-)-9-fluoro-6,7-dihydro-8-{cis-(-)-4-R-hydroxy-3-S-methylpiperidin-1-yl}-5-methyl-1-oxo-1H,5H-benzo[i, j]quinolizine-2-carboxylic acid;

S-(-)-9-fluoro-6,7-dihydro-8-{cis-(+)-4-S-hydroxy-3-R-methylpiperidin-1-yl}-5-methyl-1-oxo-1H,5H-benzo[i, j]quinolizine-2-carboxylic acid; and

S-(-)-9-fluoro-6,7-dihydro-8-(3-ethyl-4-hydroxypiperidin-1-yl)-5-methyl-1-oxo-1H,5H-benzo[i,j]quinolizine-2-carboxylic acid (mixture of cis racemate and trans racemate) and pure stereoisomers thereof.

- 10. The composition of claim 9, wherein the benzoquinolizine-2-carboxylic acid antimicrobial drug is S-(-)-9-fluoro-6,7-dihydro-8-(4-hydroxypiperidin-1-yl)-5-methyl-1-oxo-1H,5H-benzo[i,j]quinolizine-2-carboxylic acid arginine salt, or a solvatomorphic or polymorphic form thereof.
- 11. The composition of claim 9, wherein the benzoquinolizine-2-carboxylic acid antimicrobial drug is S-(-)-9-fluoro-6,7-dihydro-8-(4-hydroxypiperidin-1-yl)-5-methyl-1-oxo-1H,5H-benzo[i,j]quinolizine-2-carboxylic acid 0.2 hydrate.
- 12. The composition of claim 9, wherein the benzoquinolizine-2-carboxylic acid antimicrobial drug is S-(-)-9-fluoro-6,7-dihydro-8-(4-hydroxypiperidin-1-yl)-5-methyl-1-oxo-1H,5H-benzo[i,j]quinolizine-2-carboxylic acid.

- 13. The composition of claim 1, wherein the benzoquinolizine-2-carboxylic acid antimicrobial drug comprises about 0.1% to about 1.0 % by weight of the composition.
- 14. The composition of claim 1, wherein the amino acid is selected from arginine, histidine, arginine acetate, arginine-glutamate, arginine monohydrochloride, histidine acetate, histidine acetate dihydrate, histidine monohydrochloride, histidine monohydrochloride monohydrate, lysine, lysine acetate, lysine monohydrochloride, ornithine, tryptophan or salts thereof.
- 15. The composition of claim 14, wherein the amino acid comprises Larginine.
- 16. The composition of claim 14, wherein the amino acid comprises L-lysine.
- 17. The composition of claim 1, wherein the cyclodextrin polymer is selected from α -cyclodextrin, β -cyclodextrin, γ -cyclodextrin, hydroxypropyl β -cyclodextrin or derivatives thereof.
- 18. The composition of claim 17, wherein the cyclodextrin polymer comprises hydroxypropyl β-cyclodextrin.
- 19. The composition of claim 1, wherein the solubilizing agent comprises about 1.5 % to about 3.5 % by weight of the composition.
- 20. The composition of claim 14, wherein the solubilizing agent is amino acid and comprises about 0.1 % to about 1.4 % by weight of the composition.
- 21. The composition of claim 17, wherein the solubilizing agent is cyclodextrin polymer and comprises about 1.5 % to about 3.5 % by weight of the composition.
- 22. The composition of claim 1, further comprising a pharmaceutically acceptable vehicle comprising a modifying agent selected from acids, bases, inorganic basic salts, organic basic salts, buffering agents or mixtures thereof and/or an agent for adjusting osmolality in amounts whereby the solution is substantially isotonic and has a physiologically acceptable pH.
- 23. The composition of claim 1, that is in a physical form selected from a concentrate, lyophilisate, powder, solution, or suspension.
- 24. A method of treating and/or preventing a bacterial infection disease in a subject comprising administering to the subject, a pharmaceutical composition of claim 1 in a therapeutically or prophylactically effective dose.

- 25. The method of claim 24, wherein the composition is diluted in a pharmaceutically acceptable liquid prior to being administered to the subject.
- 26. The method of claim 24, wherein the subject is a human or animal subject.
- 27. The method of claim 24, wherein the benzoquinolizine-2-carboxylic acid antimicrobial drug is selected from S-(-)-9-fluoro-6,7-dihydro-8-(4-hydroxypiperidin-1-yl)-5-methyl-1-oxo-1H,5H-benzo[i,j]quinolizine-2-carboxylic acid arginine salt, or solvatomorphic or polymorphic forms thereof;
- S-(-)-9-fluoro-6,7-dihydro-8-(4-hydroxypiperidin-1-yl)-5-methyl-1-oxo-1H,5H-benzo[i,j]quinolizine-2-carboxylic acid 0.2 hydrate; or
- S-(-)-9-fluoro-6,7-dihydro-8-(4-hydroxypiperidin-1-yl)-5-methyl-1-oxo-1H,5H-benzo[i,j]quinolizine-2-carboxylic acid.
- 28. The method of claim 24, wherein the daily dose is about 0.01 mg to 100 mg/kg of S-(-)-9-fluoro-6,7-dihydro-8-(4-hydroxypiperidin-1-yl)-5-methyl-1-oxo-1H,5H-benzo[i,j]quinolizine-2-carboxylic acid, its arginine salt or 0.2 hydrate thereof.
- 29. The method of claim 24, wherein the benzoquinolizine-2-carboxylic acid antimicrobial drug comprises about 0.1 to 10% by weight of the composition.
- 30. The method of claim 24, wherein said solubilizing agent is selected from the group consisting of amino acids, cyclodextrin polymers or their derivatives, or mixtures thereof.
- 31. The method of claim 24, wherein said composition is administered by intravenous injection or infusion.
- 32. The method of claim 24, wherein the route of administration is parenteral.
- A process for preparing a pharmaceutical composition comprising: mixing a pharmaceutically effective amount of benzoquinolizine-2-carboxylic acid antimicrobial drug of the formula (I) according to claim 1 with a pharmaceutically acceptable vehicle comprising a solubilizing agent at a concentration effective to maintain the drug in solution at physiologically compatible pH.
- 34. The process of claim 33, wherein said solubilizing agent is selected from amino acids, cyclodextrin polymers or their derivatives, or mixtures thereof.
- 35. The process of claim 34, wherein the benzoquinolizine-2-carboxylic acid antimicrobial drug is S-(-)-9-fluoro-6,7-dihydro-8-(4-hydroxypiperidin-1-yl)-5-methyl-1-oxo-1H,5H-benzo[i,j]quinolizine-2-carboxylic acid arginine salt, solvatomorphic or polymorphic forms thereof; S-(-)-9-fluoro-6,7-dihydro-8-(4-hydroxypiperidin-1-yl)-5-methyl-1-oxo-1H,5H-benzo[i,j]quinolizine-2-carboxylic acid 0.2 hydrate, or S-(-)-9-

fluoro-6,7-dihydro-8-(4-hydroxypiperidin-1-yl)-5-methyl-1-oxo-1H,5H-benzo[i,j]quinolizine-2-carboxylic acid.